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Uncovering the Mechanistic Role of HMPA in the Samarium Barbier Reaction

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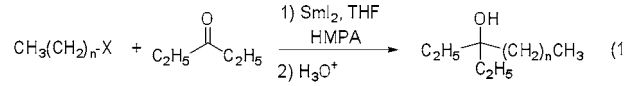
Abstract: The presence of HMPA is critical for the selective coupling of alkyl halides and ketones by SmI_2. Although previous rate studies have shown that HMPA dramatically accelerates the reduction of alkyl halides over ketones, the basis of this rate acceleration is unknown. In this communication, we report experimental and computational evidence that demonstrate that the selectivity observed in the samarium Barbier reaction is in part a result of activation of the alkyl halide bond by HMPA.

The addition of HMPA to samarium diiodide (SmI_2) has a profound impact on the reactivity and selectivity of the reagent.[1] Several groups have studied reactions initiated by SmI_2−HMPA and have uncovered a complex mechanistic role for the additive. Coordination of HMPA to SmI_2 not only produces a more powerful reductant but also displaces iodide ligands to the outer sphere of Sm^{II} creating open coordination sites for substrates while concomitantly producing a sterically encumbered reductant.[2] HMPA also plays a critical mechanistic role in post-electron-transfer events in SmI_2-mediated reactions. Addition of HMPA retards the rate of bimolecular coupling of biaryl ketyl radicals through complexation of Sm^{III} that bridges colligating radical anions.[3] Conversely, HMPA accelerates SmI_2-initiated 5-*exo*-*trig* ketyl-olefin cyclizations through conversion of the intermediate Sm(III)-ketyl radical contact ion pair to a solvent- separated ion pair.[4] Although these studies have provided critical mechanistic insight into important bond-forming reactions that occur through initial reduction of a carbonyl, there are still numerous gaps in our understanding of the mechanistic role of HMPA in the reduction of alkyl halides and reductive coupling of alkyl halides with carbonyls.

Previous mechanistic studies on the samarium Barbier reaction have shown that alkyl halides are reduced by SmI_2 to organosamarium intermediates which subsequently add to ketones producing alcohols as final products.[5] One of the intriguing features of this reaction is the selective reduction of alkyl halides over carbonyls by SmI_2 in the presence of HMPA. In the absence of HMPA, reactions are inefficient, providing mixtures of coupled and reduced products along with unreacted starting material.[6] Conversely, reactions containing 8 or more equivalents of HMPA (based on [SmI_2]) provide Barbier products exclusively.[6] Kinetic studies on the reduction of primary and secondary alkyl iodides and dialkyl ketones show that reduction of all substrates by SmI_2 is slow. Upon the addition of HMPA to reactions, the rates of reduction of alkyl iodides increase nearly 4 orders of magnitude whereas the increase in the rate of dialkyl ketone reduction is significantly less pronounced.[7] The increased rate of alkyl halide reduction by SmI_2 upon the addition of HMPA results in the selective coupling observed in samarium Barbier reactions, but the basis of this effect is unknown. Given recent findings on the role of HMPA in post-electron-transfer steps, could HMPA be playing a mechanistic role beyond coordination to SmI_2 and production of a more powerful reductant?

To test this question, a series of rate studies was performed on reactions of 1-iodododecane (**1**) and 1-bromodecane (**2**) with 3-pentanone (**3**) to determine the rate orders of the individual components in the samarium Barbier reaction shown in eq 1. Rate studies were performed under pseudo-first-order conditions with



1 n = 11; X = I
2 n = 9; X = Br
3
4 n = 11
5 n = 9

the substrates in excess with respect to SmI_2 whose decay was monitored at 550 nm. The rate constants for reduction and the rate orders for all components are shown in Table 1. Rate orders of one for SmI_2 and alkyl halide and zero for **3** are consistent with previous studies of the Barbier reaction.[5−7] Surprisingly, the rate order of HMPA was first order (1.0 ± 0.1) for the reaction of **1** and **3** and nearly first order (0.8 ± 0.1) for the reaction of **2** and **3**.

Table 1. Rate Orders for Alkyl Halide, **3**, SmI_2, and HMPA

	Rate Order				
Alkyl halide	RX[a]	**3**[b]	SmI_2[c]	HMPA[d]	k (M^{-1} s^{-1})
1	1.1 ± 0.1	0	1.0 ± 0.1	1.0 ± 0.1	4.3 ± 0.2
2	0.96 ± 0.01	0	1.0 ± 0.1	0.8 ± 0.1	0.15 ± 0.01

[a] [SmI_2] = 5 mM; [HMPA] = 50 mM; [**1**] = 45−260 mM; [**2**] = 50−300 mM. [b] [SmI_2] = 5 mM; [**1**] = 110 mM; [**2**] = 125 mM; [HMPA] = 50 mM; [**3**] = 50−300 mM. [c] Fractional time method (see Supporting Information). [d] [SmI_2] = 5 mM; [HMPA] = 10−160 mM; [**1**] = 110 mM; [**2**] = 125 mM; [**3**] = 125 mM.

To further explore the effect of HMPA, the rates of reduction of **1** and **2** in the presence and absence of **3** were monitored with increasing concentrations of HMPA from 0−300 equiv with respect to SmI_2 (Figure 1). The results of this experiment show two important characteristics: (1) the impact of HMPA on the rate of

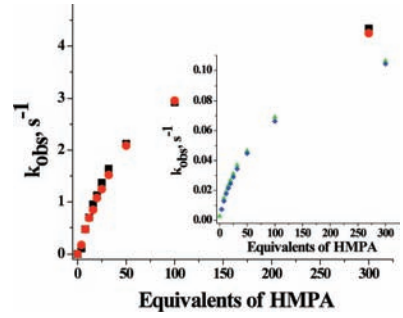


Figure 1. Equivalents of HMPA versus k_{obs} for the reduction of **1** in the presence (■; black) and absence (●; red) of **3**. The inset shows equivalents of HMPA versus k_{obs} for the reduction of **2** in the presence (◆; blue) and absence (▲; green) of **3**. [SmI_2] = 5 mM; [**1**] = 110 mM; [**2**] = 125 mM; [**3**] = 125 mM.

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reduction of **1** and **2** increases linearly up to 32 equiv and saturates only at very high concentrations of the additive, and (2) the presence of the ketone does not affect the rate of reaction over a broad range of [HMPA].

Previous studies have shown that the addition of 10 equiv of HMPA to SmI_2 produces the octahedral complex $[Sm(HMPA)_6]I_2$.[8] This complex has been shown to be a more powerful reductant when compared to SmI_2 alone.[2a,b] If the only role of HMPA in the Barbier reaction is to increase the reducing power of SmI_2 through coordination, then the rate enhancements shown in Figure 1 would be expected to reach a plateau at concentrations closer to 10 equiv. However, the first order behavior of HMPA up to 32 equiv and the large amount required to achieve saturation indicate that the additive is playing an ancillary role in the reaction. Furthermore, the reduction of carbon halide bonds by SmI_2 proceeds through dissociative electron transfer and this first step of the reaction is rate-limiting.[7,8a] Given these observations, it is difficult to envision a post-electron-transfer role for HMPA.

Lewis base activation provides a useful method for accelerating reactions.[9] Although Lewis base activation of alkyl halide bonds has not been explored in detail, this approach has been applied to several important processes and is best exemplified by the elegant work of Denmark and co-workers.[10] In the late 1960s, Wigfield proposed that the ratios of C vs O alkylation of the anion of ethylacetoacetate was a result of the interaction between solvent (HMPA or DMSO) and alkyl halides.[11] He proposed an S_N2 type complex, involving interaction of the nucleophilic oxygen of solvent with the halogen bearing carbon of the alkyl halide. Formation of the complex was rationalized on the basis of changes in the P═O (or S═O) bond stretching frequency to lower wave numbers in the presence of a range of alkyl halides. Although the hypothesis of Wigfield is reasonable, it is also possible that the shifts in P═O (or S═O) stretching frequencies could result from a generalized solvent dielectric effect. Given these findings, could the kinetic behavior of HMPA in the samarium Barbier reaction possibly result from Lewis base activation through interaction of HMPA with the alkyl halide?

To further investigate the degree of interaction between HMPA and alkyl halides in THF, a series of ^1H and ^{13}C NMR titration experiments were carried out through successive addition of HMPA to either iodoethane or bromoethane in d_8-THF. Upon addition of 1 equiv of HMPA to iodoethane, the ^1H chemical shift of the methylene bearing the halide shifted downfield by 0.008 ppm. Addition of a second equivalent of HMPA led to a further downfield shift of 0.014 ppm. In ^{13}C NMR experiments on the same substrate, the chemical shift values for the addition of 1 and 2 equiv of HMPA shifted downfield by 0.087 and 0.174 ppm respectively. Similar but less pronounced effects were observed for bromoethane (see Supporting Information). These results are consistent with interaction between HMPA and alkyl halides.

To explore the degree of interaction between HMPA and an alkyl halide, DFT calculations were carried out using Gaussian03.[12] Bromoethane was chosen as the model substrate for ease of computation. Optimization of all structures was performed under tight optimization conditions employing a B3LYP[13a] hybrid functional with the 6-311+G(d,p) basis set.[13b] To model solvent effects, single-point energy calculations were performed on the gas phase optimized geometries using the Onsager[14] model with THF as the solvent ($\epsilon = 7.58$). A complex between bromoethane and HMPA was identified on the potential energy surface that was more stable than the individual components by 3.2 kcal/mol after the addition of ZPVE corrections as shown in Figure 2 (see Supporting Information).

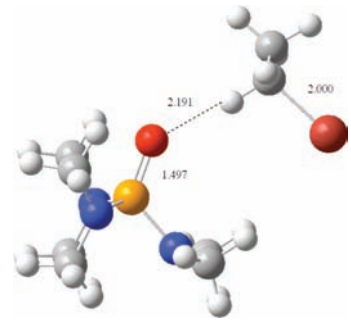


Figure 2. Calculated gas phase complex between HMPA and bromoethane. Colors indicate the following: Gray, C; Blue, N; Red, O; Dark Red, Br; Orange, P; and White, H. The distances marked are in angstrom units.

Scheme 1

$$\text{R-X} + \text{HMPA} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{HMPA--R--X}]$$

$$[\text{HMPA--R--X}] + \text{Sm}^{\text{II}}(\text{HMPA})_m \xrightarrow{k_2} \text{R}^{\bullet} + \text{Sm}^{\text{III}}(\text{HMPA})_m + \text{X}^{-} + \text{HMPA}$$

Elongation of the C−Br bond of bromoethane from 1.987 to 2.000 Å as well as the P═O bond from 1.492 to 1.497 Å of HMPA was observed for the complex, indicating a significant interaction between the two reactants. Furthermore, Mulliken charges calculated for the complex show significant polarization of the C−X bond of bromoethane as well as the P═O bond of HMPA in the complex (see Supporting Information). The Mulliken charges on the methylene bearing the bromide change from −0.262 to −0.254 in the complex. The deshielding effects observed in the ^{13}C NMR experiments are consistent with this finding. Polarization of the carbon halide bond increases the reactivity of the substrate thus facilitating its reduction by [SmI_2−HMPA]. The computational results reveal a possible additional role for HMPA in the samarium Barbier reaction.

The spectroscopic, kinetic, and computational data provide the following details about the samarium Barbier reaction: (1) The rate of reaction is zero order in ketone and first order in alkyl halide, SmI_2, and HMPA. (2) At high concentrations, HMPA displays saturation behavior. (3) Interaction of HMPA with an alkyl halide leads to elongation of the carbon−halide bond making it more susceptible to reduction. The question that remains is: Does carbon−halide bond activation by HMPA explain the saturation kinetics displayed by HMPA? Scheme 1 shows the initial activation of the carbon−halide bond by HMPA and the subsequent reduction of the RX−HMPA complex. Equation 2 is the overall rate expression for the samarium Barbier reaction where $[RX]_T = [RX] + [RX{-}HMPA]$ because both the alkyl halide

$$-\frac{\mathrm{d}[SmI_2]}{\mathrm{d}t} = \frac{k_2[Sm^{II}(HMPA)_m][RX]_T[HMPA]}{\frac{k_{-1} + k_2[Sm^{II}(HMPA)_m]}{k_1}[HMPA]} \qquad (2)$$

and the complex are susceptible to reduction. If we assume that the initial single-electron reduction is rate limiting, then $k_2[Sm^{II}(HMPA)_m] \ll k_{-1}$ giving eq 3 where K_d (k_{-1}/k_1) is the

$$-\frac{\mathrm{d}[SmI_2]}{\mathrm{d}t} = \frac{k_2[Sm^{II}(HMPA)_m][RX]_T[HMPA]}{K_d + [HMPA]} \qquad (3)$$

dissociation constant of the R--X--HMPA complex and $k_2[Sm^{II}(HMPA)_m][RX]_T = V_{max}$.

To confirm the viability of eq 3 as a representation of the system, the data shown in Figure 1 (and the inset) were fit to eq 4, where V_{max}, K_d, and n are obtained. The data obtained from the

$$k_{obs} = \frac{V_{max}[HMPA]^n}{K_d + [HMPA]^n} \quad (4)$$

fit are contained in Table 2.

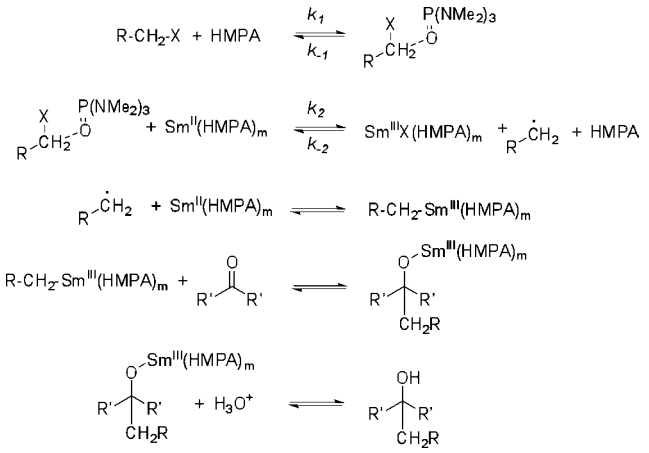
Table 2. Fit of Experimental Data to Eq 4[a]

Alkyl halide	V_{max} (M^{-1} s^{-1})	K_d (M)	n[b]
1	5.5 ± 0.3	0.41 ± 0.08	0.99 ± 0.06
2	0.18 ± 0.01	0.9 ± 0.2	0.79 ± 0.04

[a] The fit for each system to eq 4 provided an $r^2 > 0.997$. [b] Order of HMPA.

The rate order for HMPA obtained from eq 4 is the same as that acquired from an ln[HMPA] vs ln k_{obs} plot of the linear region of the data contained in Figure 1. Of particular importance is the K_d of the complex of HMPA and alkyl halides **1** and **2** (0.41 ± 0.08 and 0.92 ± 0.15 M, respectively). These data show that HMPA has a higher affinity for alkyl iodides than alkyl bromides, consistent with previous studies of Wigfield.[11] On the basis of our kinetic and computational studies as well as previous work contained in the literature, we propose the detailed mechanism shown in Scheme 2. Under Barbier conditions (where all reaction components are mixed in one flask), coordination of HMPA to SmI_2 produces $Sm^{II}(HMPA)_m$ and interaction of the remaining HMPA with the alkyl halide produces an intermediate that is reduced by the $Sm^{II}(HMPA)_m$ complex in the rate-limiting step of the reaction. Reduction of the resultant radical produces an organosamarium intermediate that attacks the electrophilic carbon of the ketone.[5] Subsequent workup produces the final alcohol product.

Scheme 2



In conclusion, the results presented herein show that HMPA plays a complex mechanistic role in the samarium Barbier reaction. While it is recognized that addition of HMPA to SmI_2 increases the reducing power of Sm^{II}, the key finding of this study is the importance of HMPA in the activation of carbon−halide bonds. This interaction of HMPA with alkyl halides leads to elongation of the carbon−halide bond making it more susceptible to reduction, thus providing the basis for the selective reduction responsible for the success of the samarium Barbier reaction. While these studies explain the impact of HMPA in this particular reaction, these results may have an important impact for the activation of bonds in other electron transfer processes.[15] We are currently examining this supposition, and results of these studies will be reported in due course.

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Supporting Information Available: General experimental methods, spectroscopic, rate data, Cartesian coordinates of all optimized structures and their corresponding energies. Complete ref 12. This material is available free of charge via the Internet at http://pubs.acs.org.

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